

WHAT IS CLAIMED IS:

~~1/ A method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate linkages, phosphorothioate linkages, and phosphorodithioate linkages;~~

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula $D^+ E^-$ wherein:

D⁺ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

Et is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

2. The method of claim 1 wherein said neutralizing agent is a salt of formula

20 D^+E^- .

3. The method of claim 2 wherein E⁻ is a tetrazolide anion.

4. The method of claim 1 wherein E is 1H-tetrazolide anion, 5-methylthio-1H-tetrazolide anion, 5-ethylthio-1H-tetrazolide anion or 1-phenyl-5-thiol-1H-tetrazolide anion.

25 5. The method of claim 1 wherein E⁻ is 1H-tetrazolide anion.

6. The method of claim 3 wherein D^+ is a protonated form of any of an alkyl,

alkenyl or alkynyl amine having from one to about 20 carbons, an aliphatic heterocyclic amine, an aromatic heterocyclic amine, or a guanidine.

7. The method of claim 1 wherein D^+ is a protonated form of an alkyl amine.
- 5 8. The method of claim 3 wherein D^+ is a protonated form of trimethyl amine, triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyl dimethyl amine, t-butyl dimethyl amine, diisopropylethyl amine, or N,N,N',N'-tetramethyl-1,2-diaminoethane.
- 10 9. The method of claim 3 wherein D^+ is a protonated form of an aliphatic heterocyclic amine.
- 15 10. The method of claim 3 wherein D^+ is a protonated form of any of DBU, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine, -ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5ene.
11. The method of claim 3 wherein D^+ is a protonated form of an aromatic heterocyclic amine.
- 20 12. The method of claim 3 wherein D^+ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.
13. The method of claim 3 wherein D^+ is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine.
- 25 14. The method of claim 3 wherein D^+ is a protonated form of an alkylamino substituted pyridine.

- 15 15. The method of claim 3 wherein D^+ is a protonated form of 4-dimethylaminopyridine.
16. The method of claim 3 wherein D^+ is a protonated form of guanidine.
17. The method of claim 3 wherein D^+ is a protonated form of a tetraalkyl
5 guanidine.
18. The method of claim 3 wherein D^+ is a protonated form of N,N,N',N'-tetramethylguanidine.
19. The method of claim 3 wherein D^+ is a quaternary tetraalkylammonium cation.
20. The method of claim 3 wherein D^+ is a tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation.
21. The method of claim 3 wherein E^- is 1H-tetrazolide anion.
22. The method of claim 1 wherein E^- is 4,5-dicyanoimidazolide anion.
23. The method of claim 1 wherein E^- is a substituted or unsubstituted
15 alkylsulfonate anion.
24. The method of claim 1 wherein E^- is methylsulfonate anion or trifluoromethylsulfonate anion.
25. The method of claim 1 wherein E^- is a substituted or unsubstituted
20 arylsulfonate anion.

26. The method of claim 1 wherein E^- is a methylphenylsulfonate anion or a trihalomethylphenylsulfonate anion.

27. The method of claim 1 wherein E^- is trifluoromethylphenylsulfonate anion.

5 28. The method of claim 1 wherein E^- is tetrafluoroborate anion.

29. The method of claim 1 wherein E^- is hexafluorophosphate anion.

30. The method of claim 1 wherein E^- is a trihaloacetate anion.

31. The method of claim 1 wherein E^- is trifluoroacetate anion.

10 32. The method of claim 1 wherein D^+ is a protonated form of an alkyl amine.

33. The method of claim 1 wherein D^+ is a protonated form of trimethyl amine, triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyldimethyl amine, t-butyldimethyl amine, diisopropylethyl amine, or N,N,N',N'-tetramethyl-1,2-diaminoethane.

15 34. The method of claim 1 wherein D^+ is a protonated form of an aliphatic heterocyclic amine.

35. The method of claim 1 wherein D^+ is a protonated form of any of DBU, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine, 20 -ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5ene.

36. The method of claim 1 wherein D^+ is a protonated form of an aromatic heterocyclic amine.

37. The method of claim 1 wherein D^+ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

38. The method of claim 1 wherein D^+ is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine.

39. The method of claim 1 wherein D^+ is a protonated form of an alkylamino substituted pyridine.

40. The method of claim 1 wherein D^+ is a protonated form of 4-dimethylaminopyridine.

41. The method of claim 1 wherein D^+ is a protonated form of guanidine.

42. The method of claim 1 wherein D^+ is a protonated form of N,N,N',N'-tetramethylguanidine.

43. The method of claim 1 wherein D^+ is a quaternary tetraalkylammonium cation.

44. The method of claim 1 wherein D^+ is a tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation.

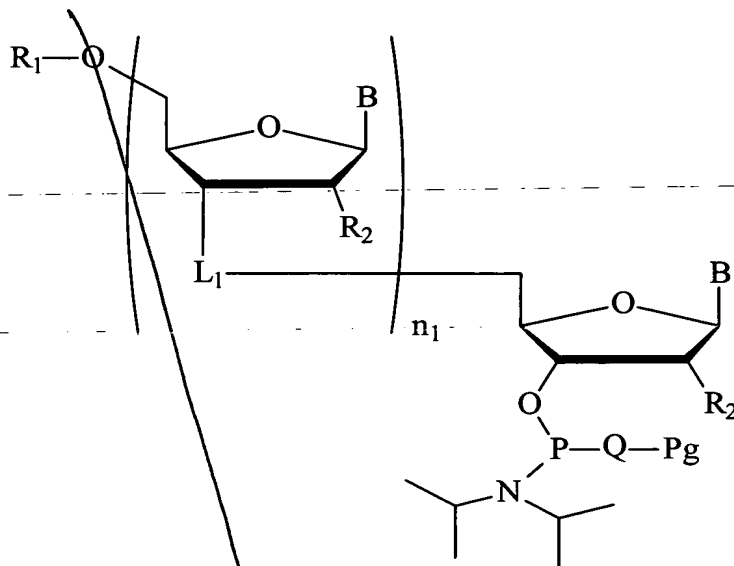
45. The method of claim 1 wherein E^- is a tetrazolide anion or substituted or unsubstituted alkylsulfonate anion, and D^+ is a tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation.

46. The method of claim 1 wherein E^- is trifluoromethanesulfonate anion and D^+ is a protonated form of N-methylimidazole, N-ethylimidazole, or 1, 2, 4-triazole.

47. The method of claim 3 wherein D^+ is a protonated form of trimethyl amine, triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyldimethyl amine, t-butyldimethyl amine, diisopropylethyl amine, N,N,N',N'-tetramethyl-1,2-diaminoethane, DBU, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine, N-ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5-ene, 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine, 4-dimethylaminopyridine, or N,N,N',N'-tetramethylguanidine, or tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation; and

E^- is 1H-tetrazolide anion, 4,5-dicyanoimidazolide anion, methylsulfonate anion, trifluoromethylsulfonate anion, methylphenylsulfonate anion, trifluoromethylphenylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or trifluoroacetate anion.

48. A method of forming an internucleoside linkage comprising reacting a phosphoramidite of formula:



wherein:

L_1 is an internucleoside linkage;

n_1 is 0 to about 100;

5 R_1 is a hydroxyl protecting group;

R_2 is a 2'-substituent group;

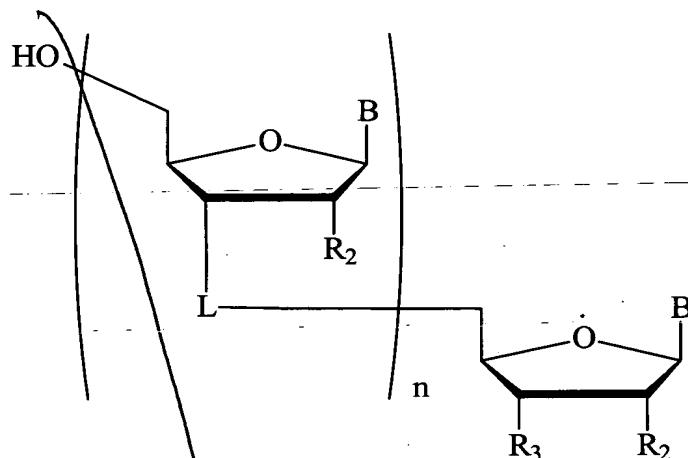
R_4 and R_5 are each independently alkyl having from 1 to about 10 carbon atoms,
or R_4 and R_5 taken together with the nitrogen atom to which they are attached form a
heterocycle;

10 B is a nucleobase;

Q is O or S;

Pg is a phosphoryl protecting group;

with a compound of formula:

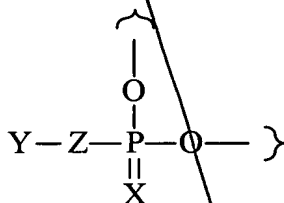


wherein

R_3 is a linker connected to a solid support;

n is from 1 to 100; and

L is an internucleoside linkage of formula:



wherein:

Z is O or S;

X is O or S; and

Y is a phosphoryl protecting group or a negative charge;

provided that at least one Y is a negative charge;

wherein said reaction is performed in the presence of a neutralizing agent;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula

D⁺ E⁻ wherein:

D⁺ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E⁻ is a tetrazolide anion, 4,5-dicyanoimidazolidine anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

49. The method of claim 48 wherein said neutralizing agent is a salt of formula D⁺ E⁻.

50. The method of claim 49 wherein E⁻ is a tetrazolide anion.

51. The method of claim 48 wherein E⁻ is 1H-tetrazolide anion, 5-methylthio-1H-tetrazolide anion, 5-ethylthio-1H-tetrazolide anion or 1-phenyl-5-thiol-1H-tetrazolide anion.

52. The method of claim 48 wherein E⁻ is 1H-tetrazolide anion.

51. The method of claim 50 wherein D⁺ is a protonated form of any of an alkyl, alkenyl or alkynyl amine having from one to about 20 carbons, an aliphatic heterocyclic amine, an aromatic heterocyclic amine, or a guanidine.

52. The method of claim 48 wherein D⁺ is a protonated form of an alkyl amine.

53. The method of claim 50 wherein D⁺ is a protonated form of trimethyl amine, triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyl dimethyl amine, t-butyl dimethyl amine, diisopropylethyl amine, or N,N,N',N'-tetramethyl-1,2-

diaminoethane.

54. The method of claim 50 wherein D^+ is a protonated form of an aliphatic heterocyclic amine.

5 55. The method of claim 50 wherein D^+ is a protonated form of any of DBU, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine, -ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5ene.

10 56. The method of claim 50 wherein D^+ is a protonated form of an aromatic heterocyclic amine.

57. The method of claim 50 wherein D^+ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

15 58. The method of claim 50 wherein D^+ is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine.

59. The method of claim 50 wherein D^+ is a protonated form of an alkylamino substituted pyridine.

20 60. The method of claim 50 wherein D^+ is a protonated form of 4-dimethylaminopyridine.

61. The method of claim 50 wherein D^+ is a protonated form of guanidine.

62. The method of claim 50 wherein D^+ is a protonated form of a tetraalkyl guanidine.

63. The method of claim 50 wherein D^+ is a protonated form of N,N,N',N' -tetramethylguanidine.

64. The method of claim 50 wherein D^+ is a quaternary tetraalkylammonium cation.

5 65. The method of claim 50 wherein D^+ is a tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation.

66. The method of claim 50 wherein E^- is 1H-tetrazolide anion.

67. The method of claim 48 wherein E^- is 4,5-dicyanoimidazolidine anion.

10 68. The method of claim 48 wherein E^- is a substituted or unsubstituted alkylsulfonate anion.

69. The method of claim 48 wherein E^- is methylsulfonate anion or trifluoromethylsulfonate anion.

15 70. The method of claim 48 wherein E^- is a substituted or unsubstituted arylsulfonate anion.

71. The method of claim 48 wherein E^- is a methylphenylsulfonate anion or a trihalomethylphenylsulfonate anion.

72. The method of claim 48 wherein E^- is trifluoromethylphenylsulfonate anion.

20 73. The method of claim 48 wherein E^- is tetrafluoroborate anion.

74. The method of claim 48 wherein E^- is hexafluorophosphate anion.
75. The method of claim 48 wherein E^- is a trihaloacetate anion.
76. The method of claim 48 wherein E^- is trifluoroacetate anion.
77. The method of claim 48 wherein D^+ is a protonated form of an alkyl
5 amine.
78. The method of claim 48 wherein D^+ is a protonated form of trimethyl
amine, triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyl dimethyl
amine, t-butyl dimethyl amine, diisopropylethyl amine, or N,N,N',N'-tetramethyl-1,2-
10 diaminoethane.
79. The method of claim 48 wherein D^+ is a protonated form of an aliphatic
heterocyclic amine.
80. The method of claim 48 wherein D^+ is a protonated form of any of DBU,
15 N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine,
N-ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-
ene, 1,4-diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5ene.
81. The method of claim 48 wherein D^+ is a protonated form of an aromatic
heterocyclic amine.
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82. The method of claim 48 wherein D^+ is a protonated form of a mono-, di-
or trialkyl pyridine that is optionally substituted with an amino group.
83. The method of claim 48 wherein D^+ is a protonated form of any of 2,4,6-
collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine,
25 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine.

84. The method of claim 48 wherein D^+ is a protonated form of an alkylamino substituted pyridine.

85. The method of claim 48 wherein D^+ is a protonated form of 4-
5 dimethylaminopyridine.

86. The method of claim 48 wherein D^+ is a protonated form of guanidine.

87. The method of claim 48 wherein D^+ is a protonated form of N,N,N',N'-
tetramethylguanidine.

88. The method of claim 48 wherein D^+ is a quaternary tetraalkylammonium
10 cation.

89. The method of claim 48 wherein D^+ is a tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation.

90. The method of claim 48 wherein E^- is a tetrazolide anion or substituted
15 or unsubstituted alkylsulfonate anion, and D^+ is a tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation.

91. The method of claim 48 wherein E^- is trifluoromethanesulfonate anion and D^+ is a protonated form of N-methylimidazole, N-ethylimidazole, or 1, 2, 4-triazole.

92. The method of claim 50 wherein D^+ is a protonated form of trimethyl amine, triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyldimethyl amine, t-butyl dimethyl amine, diisopropylethyl amine, N,N,N',N'-tetramethyl-1,2-diaminoethane, DBU, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine, N-ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-

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diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5-ene, 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine, 4-dimethylaminopyridine, or N,N,N',N'-tetramethylguanidine, or tetramethylammonium, 5 tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation; and

E⁻ is 1H-tetrazolide anion, 4,5-dicyanoimidazolide anion, methylsulfonate anion, trifluoromethylsulfonate anion, methylphenylsulfonate anion, trifluoromethylphenylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or trifluoroacetate anion.

10 93. The method of claim 50 wherein Q is O; Z is O;

Pg is β -cyanoethyl, methyl, (N-methyl-N-benzoylamino)ethyl, (N-ethyl-N-benzoylamino)ethyl, 2-[N-methyl-N-(4-methoxybenzoyl)amino]ethyl, 2-(N-isopropyl-N-benzoylamino)ethyl, 2-[N-ethyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-methyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-ethyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-(thionobenzoylamino)ethyl, 3-(thionobenzoylamino)propyl, 2-(N-phenylthiocarbamoylamino)ethyl, 2-[(1-naphthyl)carbamoyloxy]ethyl, diphenylsilylethyl, δ -cyanobutenyl, cyano *p*-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxo phenoxy ethyl; and

20 Y is β -cyanoethyl, allyl, methyl, (N-methyl-N-benzoylamino)ethyl, (N-ethyl-N-benzoylamino)ethyl, 2-[N-methyl-N-(4-methoxybenzoyl)amino]ethyl, 2-(N-isopropyl-N-benzoylamino)ethyl, 2-[N-ethyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-methyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-ethyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-(thionobenzoylamino)ethyl, 3-(thionobenzoylamino)propyl, 2-(N-phenylthiocarbamoylamino)ethyl, 2-[(1-naphthyl)carbamoyloxy]ethyl, diphenylsilylethyl, δ -cyanobutenyl, cyano *p*-xylyl, methyl-N-trifluoroacetyl ethyl, acetoxo phenoxy ethyl, or a negative charge.

94. The method of claim 48 wherein:

said neutralizing agent is a salt of formula $D^+ E^-$;

E^- is a tetrazolide anion;

D^+ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group;

5 Q is O;

 Z is O;

R_4 and R_5 are each diisopropyl, or R_4 and R_5 together with the nitrogen atom to which they are attached form morpholine;

 Pg is β -cyanoethyl, methyl, diphenylsilylethyl, δ -cyanobutenyl, cyano *p*-xylyl
10 , methyl-N-trifluoroacetyl ethyl or acetoxo phenoxy ethyl; and

 Y is β -cyanoethyl, allyl, methyl, diphenylsilylethyl, δ -cyanobutenyl, cyano *p*-xylyl , methyl-N-trifluoroacetyl ethyl or acetoxo phenoxy ethyl or a negative charge.

95. The method of claim 94 wherein:

E^- is 1H-tetrazolide anion;

15 D^+ is a protonated form of dimethylaminopyridine;

 Pg is β -cyanoethyl, diphenylsilylethyl, δ -cyanobutenyl, cyano *p*-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxo phenoxy ethyl; and

 Y is β -cyanoethyl, allyl, diphenylsilylethyl, δ -cyanobutenyl, cyano *p*-xylyl, methyl-N-trifluoroacetyl ethyl, acetoxo phenoxy ethyl or a negative charge.

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96. A method comprising the steps of:

(a) providing a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl protecting group;

25 (b) deprotecting the 5'-hydroxyl of the 5'-O-protected phosphorus-linked oligomer with a deprotecting reagent;

(c) washing the deprotected phosphorus-linked oligomer on the solid support with a solution containing a neutralizing agent;

30 (d) reacting the deprotected 5'-hydroxyl with an 5'-protected nucleoside phosphoramidite to produce a phosphite triester linkage therebetween; and

(e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage; and optionally repeating steps b through e at least once for subsequent couplings of additional nucleoside phosphoramidites;

5 wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula $D^+ E^-$ wherein:

10 D^+ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

15 E^- is a tetrazolide anion, 4,5-dicyanoimidazolidine anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

97. A method comprising the steps of:

20 (a) providing a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl protecting group;

(b) deprotecting the 5'-hydroxyl of the 5'-O-protected phosphorus-linked oligomer with a deprotecting reagent to form a support bound 5'-deprotected phosphorus-linked oligomer;

25 (c) optionally washing the deprotected phosphorus-linked oligomer on the solid support;

(d) contacting the support bound 5'-deprotected phosphorus-linked oligomer with a solution comprising a 5'-protected nucleoside phosphoramidite to produce a phosphite triester linkage therebetween, wherein said solution further comprises a neutralizing agent; and

30 (e) oxidizing or sulfurizing the phosphite triester linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage; and

optionally repeating steps b through e at least once for subsequent couplings of additional nucleoside phosphoramidites;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula $D^+ E^-$ wherein:

D^+ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E^- is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

98. A composition comprising a 5'-protected nucleoside phosphoramidite and a salt of formula $D^+ E^-$ wherein:

D^+ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E^- is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

99. The composition of claim 98 wherein:

E^- is a tetrazolide anion; and

D^+ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

100. The composition of claim 98 wherein:

E⁻ is 1H-tetrazolide anion; and

D⁺ is a protonated form of dimethylaminopyridine.

101. The composition of claim 98 further comprising a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer
5 having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl protecting group.

102. The composition of claim 99 further comprising a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl
10 protecting group.

103. The composition of claim 100 further comprising a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl protecting group.